WO 98/10786
PCT/IL97/00301

PATENT COOPERATION TREATY

30 MAR 1998

PCT

From the INTERNATIONAL BUREAU

To:

DR. YITZHAK HESS & PARTNERS
P.O. Box 6451
61063 Tel Aviv
ISRAËL

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 19 March 1998 (19.03.98)	
Applicant's or agent's file reference 7792	**IMPORTANT NOTICE**
International application No. PCT/IL97/00301	**International filing date** (day/month/year) 10 September 1997 (10.09.97)
	Priority date (day/month/year) 12 September 1996 (12.09.96)
Applicant COHEN, Yarom	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CA,CN,EP,ID,IL,JP,KP,KR,NO,PL,SK,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,HU,IS,KE,KG,KZ,LC,
   LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NZ,OA,PT,RO,RU,SD,SE,SG,SI,SL,TJ,TM,TR,TT,UA,
   UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   19 March 1998 (19.03.98) under No. WO 98/10786

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The Internati nal Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
7792		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL97/00301	10/09/1997	12/09/1996
International Patent Classification (IPC) or national classification and IPC		
A61K38/31		
Applicant		
COHEN, Yarom		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/03/1998	20. 11. 98
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Schnack, A Telephone No. (+49-89) 2399-8149

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL97/00301

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-24 as originally filed

Claims, No.:

1-58 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1(part), 51, 52(part), 56, 57, 58(part).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1(part), 51, 52(part), 56, 57, 58(part).

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1(part), 2-50, 52(part), 53-55, 58(part).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	none
	No:	Claims	1-50, 52-55, 58
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-50, 52-55, 58
Industrial applicability (IA)	Yes:	Claims	1-50, 52-55 see separate sheet, 58
	No:	Claims	none

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The documents which are referred to in this communication are consecutively numbered in the order of their listing in the International search Report.

Section IV

The IPEA considers that there are four inventions claimed in the present application; the reasons being as follows: the use of metformin in a pharmaceutical composition for the treatment of Syndrome X of Reaven has ben described in the prior art, (see Pharmacological Research, vol. 30, 1994, pages 187-228 and Cardiovascular Risk Factors, vol. 3, 193, pages 67-73. Hence, in view of the prior art, the technical problem underlying the present application can be defined as the provision of alternative pharmaceutical compositions for the treatment of Syndrome X of Reaven. The present application provides the following solutions to this problem:

1) Pharmaceutical compositions comprising Somatostatin or its analogs.
2) Pharmaceutical compositions comprising Diazoxide or its analogs.
3) Pharmaceutical compositions comprising Cyclothiazide or its analogs.
4) Pharmaceutical compositions comprising Metformin.

There exists no single inventive concept underlying the plurality of the claimed inventions in the sense of Rule 13.1 PCT. Consequently there is lack of unity of the application. Search fees has only been paid for the first claimed invention. Therefore only the claimed first invention defined by present claims 1 (partially), 2-50, 52 (partially) 53-55 and 58 (partially) has been subject for this IPER.

Section V

V.1 Novelty

Subject matter of present claims 1-7, 52-55 and 58 does not appear to be novel in the sense of Article 33(1) and (2) for the following reasons:

The pharmaceutical use of somatostatin and somatostatin analogues is already known, (see D1-D8). Therefore pharmaceutical compositions comprising somatostatin or known somatostatin analogues do not appear to be novel irrespective of the intended use. Consequently, the subject matter of claims 1-7 does not appear to be novel.

D8 discloses the use of three somatostatin analogues (see page 3, formula I-III) as lung protecting agents. Those three agents appear to be identical to the somatostatin analogues of present claim 35. Furthermore does it appear that D8 discloses at least some of the somatostatin analogues mentioned in the present claims 8-50, (compare e.g. D8, page 8, line 20 with present claim 9). Consequently it would appear that the subject matter of at least some of present claims 8-50 lacks novelty with respect to D8.

D1 discloses the use of SMS 201-995 (a somatostatin analogue) for the treatment of hyperinsulinaemia, (see introduction, and page 714, fig. 1). The present application explains that the risk factors of syndrome X of Reaven are all caused by a high resistance to insulin (cf. page 2, lines 6-9). Since hyperinsulinaemia is a hallmark of insulin resistance (see D9, page 68, 2. col. lines 7-14), it would appear that the use of somatostatin analogues according to present claims 52-55 and 58 is not novel with respect to D1.

D2 discloses the use of octreotide, an analogue of somatostatin, for the treatment of hyperinsulinaemia, (see abstract and page 754, fig. 3). For the same reasons as stated above, the subject matter of present claims 52-55 and 58 does not appear to be new with respect to D2.

D3 discloses the use of somatostatin in the treatment of hypertension in obese patients suffering from hyperinsulinaemia. Hypertension and central obesity are some of the risk factors mentioned in the present application, (cf. page 1, last paragraph). D3 suggests that these risk factors may be linked to hyperinsulinaemia, (which is a characteristic of insulin resistance), and therefore it would appear that the subject matter of present claims 52-55 and 58 is not novel with respect to D3.

D4 discloses the use of SMS 201-995 (octreotide acetate) for the treatment of hyperinsulinism in infants. With respect to D4, the subject matter of present claims 52-55 and 58 therefore does not appear to be new.

D5 discloses the use of SMS 201-995 (octreotide acetate) in the treatment of unstable angina. Since this disease is one of indications embraced by present claims 52-55 and 58 (cf. present description page 21, line 25), the subject matter of these claims also does not appear to be novel with respect to D5.

D6 and D7 disclose somatostatin analogues, which inhibit the release of insulin (see abstracts). With respect to these documents, it would therefore appear that subject matter of present claims 52-55 and 58 is not novel, because it appears that it is the capacity of somatostatin and analogues to inhibit the insulin secretion, which is responsible for the therapeutic effect in patients suffering from hyperinsulinaemia.

V.2 Inventive step

Problem of the invention appears to be the provision of a therapeutic agent for the treatment of hyperinsulinemia, (cf. present description, page 1, lines 1-17). This problem is solved by the use of somatostatin analogues. However, this solution to the problem appears to be obvious to the person skilled in the art for the following reason. From D1, D2, D3, D4, D5, D6 and D7 it is known that somatostatin and analogues (e.g. octreotide) can be used in the treatment of hyperinsulinemia. Therefore it does not appear to be surprising that novel somatostatin analogues similar to the somatostatin analogues known from D8, also possess this therapeutic effect.
This opinion also appears to be supported by the fact that only the therapeutic effect of the known analogue octreotide has been shown, without providing any evidence that novel somatostatin analogues falling within the scope of present claims 8-50 would possess unexpected effects. Also does the present application not provide any examples of how to prepare any of the claimed compositions.

V.3 Industrial applicability

For the assessment of the present claims 52-55 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII:

It appears evident from the description, (page 4, lines 18-20) that the somatostatin analogues should comprise the chain D-Trp-Lys. However, when compared to e.g. present claim 28, it appears that Trp can also be in the L-form. This inconsistency results in lack of clarity contrary to Article 6 PCT.

The term "risk factors of syndrome X of Reaven" used in present clams 1, 52 and 58 appears to be unclear, because it is not evident from the claims which factors are meant (Article 6 PCT).

It appears that present claims 2 and 3 lack a dependency reference to the independent claim 1.

The meaning of the "(as herein defined)" mentioned in present claims 1-51 and 58 is unclear, (Rule 6.2a PCT).

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 March 1998 (19.03.98)	
International application No. PCT/IL97/00301	**Applicant's or agent's file reference** 7792
International filing date (day/month/year) 10 September 1997 (10.09.97)	**Priority date** (day/month/year) 12 September 1996 (12.09.96)
Applicant COHEN, Yarom	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 March 1998 (02.03.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Martine Lee
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
7792		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IL 97/00301	10/09/1997	12/09/1996
Applicant		
COHEN, Yarom		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ **Certain claims were found unsearchable** (see Box I).

2. ☒ **Unity of invention is lacking** (see Box II).

3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - ☐ filed with the international application.
   - ☒ furnished by the applicant separately from the international application,
     - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - ☐ Transcribed by this Authority

4. With regard to the **title,**
   - ☒ the text is approved as submitted by the applicant.
   - ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - ☒ the text is approved as submitted by the applicant.
   - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - ☐ as suggested by the applicant.
   - ☐ because the applicant failed to suggest a figure.
   - ☐ because this figure better characterizes the invention.
   - ☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 97/00301

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1(part.), 2-50 (comp.), 52(part.), 53-55(comp.), 58(part.)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1 (partially), 2-50 (completely), 52 (partially), 53-55 (completely), 58 (partially)

Pharmaceutical compositions for the treatment of the risk factors of syndrome X of Reaven comprising Somatostatin or one of its analogs; Uses of the said Somatostatin compositions.

2. Claims: 1 (partially), 51 (completely), 52 (partially), 56 (completely), 58 (partially)

Pharmaceutical compositions for the treatment of the risk factors of syndrome X of Reaven comprising diazoxide or one of its analogs; Uses of the said diazoxide compositions.

3. Claims: 1 (partially), 52 (partially), 58 (partially)

Pharmaceutical compositions for the treatment of the risk factors of syndrome X of Reaven comprising cyclothiazide or one of its analogs; Uses of the said cyclothiazide compositions

4. Claims: 1 (partially), 52(partially), 57 (completely), 58 (partially)

Pharmaceutical compositions for the treatment of the risk factors of syndrome X of Reaven comprising Metformin; uses of the said metformin compositions.

INTERNATIONAL SEARCH REPORT

Internat[redacted]pplication No
PCT/IL 97/00301

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/31 A61K31/54 A61K31/155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHILLIPS R.E. ET AL: "Effectiveness of SMS 201-995, a synthetic, long-acting somatostatin analogue, in treatment of quinine-induced hyperinsulinaemia" LANCET THE, vol. 1, 1986, LONDON GB, pages 713-715, XP002053032 see the whole document ---	1-50, 52-55,58
X	BOYLE P.J. ET AL: "Octeotride reverses hyperinsulinaemia and prevents hypoglycemia induced by sulfonilurea overdoses" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 76, no. 3, 1993, pages 752-756, XP002053033 see the whole document ---	1-50, 52-55,58

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 1998	09.07.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fernandez y Branas,F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CARRETTA, R. ET AL: "Reduction of blood pressure in obese hyperinsulinaemic hypertensive patients during somatostatin infusion" JOURNAL OF HYPERTENSION SUPPLEMENT, vol. 7, 1989, pages s196-s197, XP002053034 see the whole document ---	1-50, 52-55,58
X	KIRK, J.M.W. ET AL: "Somatostatin analogue in short term management of hyperinsulinism" ARCHIVES OF DISEASE IN CHILDHOOD, vol. 63, no. 12, 1988, page 14931494 XP002053035 see the whole document ---	1-50, 52-55,58
X	BLUMING A.Z. ET AL: "Successful treatment of unstable angina in malignant carcinoid syndrome using the long acting somatostatin analogue SMS 201-995 (sandostatin)" THE AMERICAN JOURNAL OF MEDICINE, vol. 85, 1988, pages 872-874, XP002053036 see the whole document ---	1-50, 52-55,58
X	US 4 100 153 A (GARSKY V.M.) 1978 see the whole document ---	1-50, 52-55,58
X	US 4 159 263 A (GARSKY VICTOR M) 26 June 1979 see the whole document ---	1-50, 52-55,58
X	EP 0 374 089 A (SANDOZ AG) 20 June 1990 see the whole document ---	1-50
A	RAYNOR K ET AL: "Cloned somatostatin receptors: identification of subtype-selective peptides and demostration of high affinity binding of linear peptides" MOLECULAR PHARMACOLOGY, vol. 43, no. 6, June 1993, pages 838-844, XP000676382 ---	1-50, 52-55,58
A	RAYNOR K ET AL: "Characterization of cloned somatostatin receptors SSTR4 and SSTR5" MOLECULAR PHARMACOLOGY, vol. 44, no. 2, August 1993, pages 385-392, XP000644418 see the whole document --- -/--	1-50, 52-55,58

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SIRTORI C.R. ET AL: "Re-evaluation of a biguanide, Metformin: mechanism of action and tolerability" PHARMACOLOGICAL RESEARCH, vol. 30, no. 3, 1994, pages 187-228, XP002053037 see the whole document ---	
A	SMITH U.: "Clinical and therapeutical aspects of the insulin resistance syndrome" CARDIOVASCULAR RISK FACTORS, vol. 3, no. 1, 1993, pages 67-73, XP002053038 see the whole document ---	
A	GUILLAUME G. ET AL: "Syndrome X et médecine générale" REVUE MEDICALE DE BRUXELLES, vol. 16, no. 2, 1995, XP002053039 see the whole document -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna[redacted] Application No
PCT/IL 97/00301

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4100153 A	11-07-78	NONE	
US 4159263 A	26-06-79	NONE	
EP 0374089 A	20-06-90	AU 4453589 A	17-05-90
		BE 1003762 A	09-06-92
		CH 680571 A	30-09-92
		DE 3937539 A	31-05-90
		DK 562289 A	12-05-90
		FR 2638968 A	18-05-90
		GB 2225532 A,B	06-06-90
		IT 1237437 B	04-06-93
		JP 2149528 A	08-06-90
		NL 8902785 A	01-06-90
		SE 8903764 A	09-07-90

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DR. YITZHAK HESS & PARTNERS
P.O. Box 6451
61063 Tel Aviv
ISRAEL

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20. 11. 98
Applicant's or agent's file reference: 7792	**IMPORTANT NOTIFICATION**
International application No.: PCT/IL97/00301	International filing date *(day/month/year)*: 10/09/1997
Priority date *(day/month/year)*: 12/09/1996	
Applicant: COHEN, Yarom	

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Senkel, H Tel. (+49-89) 2399-8071

Form PCT/IPEA/416 (July 1992)